39. (**Amended**) The method of claim 29, wherein said degenerative disorder is selected from ~~a group consisting of~~ Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Pick's disease, Huntington's disease, multiple sclerosis, neuronal damage resulting from anoxia-ischemia, neuronal damage resulting from trauma, and neuronal degeneration associated with a natural aging process.

40. (**Amended**) A method of claim 29, further comprising administering to said patient ~~a therapeutically effective~~ an amount of a growth factor having neurotrophic activity, wherein said growth factor enhances ~~capable of enhancing~~ the effect of the ~~hedgehog~~ treatment.

41. (**Amended**) The method of claim 40, wherein said growth factor is ~~selected from a group consisting of~~ a nerve growth factor, ciliary neurotrophic growth factor, schwanoma-derived growth factor, glial growth factor, striatal-derived neuronotrophic factor, and platelet-derived growth factor.

REMARKS

Claims 1-3, 5-15, and 17-53 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that the amendments filed 7/5/01 have been entered, claims 1-41 were pending, and that claims 8-10, 19-21, 27, and 28 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter.

4. Applicants have amended the specification to correct the deficiency noted by the Examiner.

5-6. Claims 1-7, 11-18, 22-26, and 29-41 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

Applicants have amended claims reciting "effective amount" or "therapeutically effective amount" as suggested by the Examiner, thereby overcoming this ground of rejection. Applicant submits that the scope of these claims is unaltered by this amendment.

Applicants have cancelled claims 3, 4, 15, and 16, solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

Applicants have eliminated use of the term 'bioactive fragment', instead defining the function of fragments as binding a naturally occurring *patched* receptor. Applicants submit that this amendment overcomes the rejection as it relates to the term 'bioactive fragment'.

7-8. Claims 4 and 16 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants have cancelled these claims, thereby rendering this rejection moot, solely to expedite prosecution of the remaining claims. Applicants reserve the right to prosecute claims of similar or differing scope in subsequent applications.

9. Claims 1-7, 11-18, 22-26, and 29-41 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the office action alleges that the specification fails to provide enablement for *hedgehog* polypeptides other than sonic hedgehog; fails to provide enablement for fragments other than N-terminal fragments; fails to provide enablement for promoting growth, differentiation, and/or survival of cells other than embryonic cells; and fails to provide guidance for methods of treating animals using the claimed *hedgehog* polypeptides. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The first facet of this rejection is that Applicants have allegedly failed to provide enablement for fragments other than N-terminal fragments. To expedite prosecution, Applicants

have amended the claims to specify that the *hedgehog* fragments are N-terminal fragments. Additionally, Applicants have amended the claims to explicitly point out that the *hedgehog* fragments are bioactive fragments characterized by the ability to bind the *hedgehog* receptor *patched*. Such amendments are not made in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of the rejection is requested.

The second facet of this rejection is that Applicants have allegedly failed to provide enablement for promoting growth, differentiation, and/or survival of cells other than embryonic cells. Applicants traverse this rejection. At the time of filing, Applicants appreciated that the *hedgehog* polypeptides of the invention could affect both embryonic and adult tissues. "Another aspect of the present invention relates to a method of inducing and/or maintaining a differentiated state, enhancing survival, and/or promoting proliferation of a cell responsive to a vertebrate *hedgehog* protein." (page 58, lines 29-31). "[Y]et another aspect of the present invention concerns the therapeutic application of a *hedgehog* protein or a mimetic to enhance survival of neurons and other neuronal cells in both the central nervous system and the peripheral nervous system. The ability of the *hedgehog* protein to regulate neuronal differentiation during development of the nervous system and also presumably in the adult state indicates that certain of the *hedgehog* proteins can be reasonably expected to facilitate control of adult neurons." (page 63, lines 13-19). Furthermore, the disclosure discusses in detail exemplary neurological conditions that may be treated with the *hedgehog* polypeptides of the invention (page 63, line 22-page 66, line 6).

In further support of the enablement of claims directed to promoting growth, differentiation, and/or survival of cells other than embryonic cells, Applicants submit the declaration of Hank Dudek. The declaration of Hank Dudek summarizes the results of experiments in which adult tissues were treated with sonic hedgehog or desert hedgehog. Exhibit A shows that Shh and Dhh induce gli-1 expression in endoneurial fibroblasts isolated from adult rat sciatic nerve. Exhibits B and C show that Shh and Dhh improve recovery from sciatic nerve crush injuries in adult mice. Exhibit D shows that the administration of a lipid-modified Shh induces gli-1 in the adult rat striatum. Exhibits E and F show that administration of Shh attenuates malonate-induced lesions in adult rats. Each of these results demonstrates the

effects of *hedgehog* treatment in adult tissues. Additionally, these results support Applicants' contention that *hedgehog* family members have the same effects, with differing potencies, in adult models.

The observation that *hedgehog* family member have the same effects on a variety of tissues, albeit with varying potencies, has been further confirmed by Pathi et al. (Pathi et al., 2001, enclosed herewith as Exhibit 1). Pathi et al. examine the effects of Shh, Ihh, and Dhh in many different cell-based and tissue-based assays. Their results demonstrate that all three *hedgehog* family members have the same effects in these assays, and the differences lie only in their potency. Pathi et al. shows that the three *hedgehog* family members bind to the receptor *patched* with comparable IC50 values (Pathi et al., 2001, page 108, column 2 and Figure 2). Furthermore, the three family members show similar results when assayed in a cell-based system using C3H10T1/2 cells (Pathi et al., 2001, Figure 3). Finally, Pathi et al. examined the effects of the three *hedgehog* family members in a variety of tissue-based assays. These studies demonstrated that the *hedgehog* proteins have the same effects, with differing potencies, in the lateral plate, limb bud, nervous system, and in bone (Pathi et al., 2001, Figures 4, 5, 6, 7, and Table 1). The results bolster Applicants' contention that the three *hedgehog* family members "have an equivalent capacity to induce specific biological responses in vivo." (Pathi et al., 2001, page 108, column 1).

Finally, the claims are rejected for allegedly failing to enable for methods of treating animals using the *hedgehog* polypeptides of the invention. Applicants traverse this rejection. Applicants refer to the declaration of Hank Dudek which provides evidence demonstrating that *hedgehog* polypeptides improve recovery in adult rats following sciatic crush injury. This evidence supports Applicants predictions that *hedgehog* polypeptides can be used to treat neuronal disease or injury.

Applicants submit that in light of the disclosure, the declaration of Hank Dudek, and the findings of Pathi et al., the amended claims are enabled throughout their scope. Accordingly, reconsideration and withdrawal of this rejection is requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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